REMARKS

Applicant respectfully requests reconsideration. Claims 42-53 and 56-78 were previously pending in this application. No claims have been amended, canceled or added. As a result, claims 42-53 and 56-78 are pending for examination with claims 42 and 71 being independent claims. No new matter has been added.

Rejections under 35 U.S.C. §112

The Examiner rejected claim(s) 42-67 and 68-78 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. It is believed that the rejection was intended to recite claims 42-53 and 56-78.

Summary:

The rejection of all the claims, including the newly presented claims, for lack of enablement has been maintained. Applicants disagree. In response to Applicants prior remarks the Examiner has picked a few specific points to address. Applicants provide a detailed discussion on each of these points below. The Examiner also introduced several new references in support of the unpredictability of the claimed invention. Applicants have addressed each of those references below as well. However, prior to addressing the specific points Applicants present a brief summary below of the enablement issue.

Initially a prima facie rejection of the claims for a lack of enablement has not been made. As described in the prior response to office action and in more detail below, no evidence of record established the unpredictability of the claimed invention. The only objective evidence presented by the Examiner of unpredictability of the invention was the citation of Agrawal et al., and Crooke and now the citation of references teaching that cancer therapies in general are not predictable. Of these references the only one that relates specifically to the use of CpG oligonucleotides is Agrawal et al, which is a post-filing reference. Agrawal et. al., is a scientific article describing the therapeutic potential of CpG DNA. The authors have taught that they can design second generation CpG DNA with specific cytokine properties. The statements identified within the paper do not support a finding of lack of enablement of Applicants earlier invention. The cited references are not sufficient to support a finding of unpredictability. Even if a prima facie rejection had been made, Applicants

presented a rebuttal of such rejection, sufficient to overcome the rejection, in the Amendment dated April 20, 2006. In that Amendment, Applicants provided compelling evidence to demonstrate why the cited references don't support unpredictability of the claimed invention. Applicants also presented a summary of human clinical trials to further rebut the rejection. Additionally Applicants presented a summary of the data presented in the patent application and explained how it supported the enablement of the claimed invention. It is requested that the rejection be withdrawn.

Specific Issues addressed in the Office Action:

1. Reply to Applicants Arguments

Agrawal et al

The Examiner has acknowledged the scope of claim 42 but has stated that "however it is recognized in the art (as stated in the previous office action), there exists a high unpredictability of using CpG molecules in the treatment of cancer in humans." (Office Action Page 5 lines 5-6). Applicants disagree that there exists a high unpredictability of using CpG molecules in the treatment of cancer in humans. The Examiner has not provided the evidence to support such a finding.

The Examiner has the initial burden of establishing the reasons for lack of enablement. The Examiner must present evidence or explain why the accuracy of Applicants' assertions are doubtful. See MPEP section 2164.04:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC 112 first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the

> truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370."

In the instant case there is absolutely no evidence of record to establish this "high unpredictability." The Examiner has not met his burden in establishing the rejection for lack of enablement. Mere conclusions as to "the high unpredictability of using CpG oligonucleotides in the treatment of cancer" is not sufficient.

It is unclear from the statement of the Examiner whether he is referring to the predictability in the art at the time the patent application was filed or at the time Agrawal et. al., was published. At the time that the priority application was filed the recognition that a CpG motif conferred immunostimulatory properties on an oligonucleotide was not known. The inventors discovered that oligonucleotides containing unmethylated CpG dinucleotides provoked an immune response. The inventors provided significant amounts of data testing many CpG containing oligonucleotides having different sequences as well as oligonucleotides that did not contain a CpG motif. The evidence in the application clearly established a pattern of immune stimulation by this class of oligonucleotides which was consistent with the treatment of cancer. The teachings of Agrawal et. al., do not call into question that one of skill in the art would have accepted the teachings of the specification made by Applicants at the time the patent application was filed. Rather, Agrawal et. al., describes the production of a second generation of molecules having optimal stimulatory properties.

The examiner has pointed to a couple of general statements in Agrawal et. al., that suggest additional experiments could be done. For instance, the Examiner has indicated that Agrawal et al says "that the studies on the medicinal chemistry of CpG DNA have just begun.....further fine-tuning the immunomodulatory effects." The Examiner has also stated "Thus, contrary to the applicants arguments, Agrawal et. al., does support the unpredictability in the art of by teaching that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species and

that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known." (Office Action page 5 lines 14-19.)

Applicants point out that this is simply an opinion expressed by the authors that more research should be performed to better understand and optimize these drugs. These statements are not sufficient to demonstrate lack of enablement. Further research needs to be performed on many FDA-approved drugs. Biotechnology research is continually evolving. The law does not require, for a claim to be enabled, that further research to elucidate mechanisms of action, clinical preferences, etc., need to be performed. The reference by Agrawal et al. is a review article summarizing *in vitro* and *in vivo* work as well as the use of CpG in clinical trials. The authors confirm the therapeutic value of CpG oligonucleotides and discuss studies which have led to the optimization of a second generation of molecules. It is unclear how the statements cited by the Examiner render the use of CpG oligonucleotides in the treatment of cancer highly unpredictable. The fact that several clinical trials have been or are currently being conducted using CpG oligonucleotides for the treatment of cancer, strongly suggests otherwise.

On Page 6 the Examiner concludes that "it is nearly impossible to predict the claimed invention from the information provided in the specification." (Office Action page 6 lines 2-4) There is no evidence of record to demonstrate how it is nearly impossible to predict the claimed invention from the information provided in the specification. In the specification Applicants taught that oligonucleotides containing an unmethylated CpG dinucleotide produced an immune response that is consistent with the treatment of cancer. Applicants taught routes of administration. Applicants provided numerous examples of oligonucleotides falling within the genus of molecules. Significant amounts of data demonstrating the specific effects of CpG oligonucleotides are provided in the specification. Some of the data even confirms the specificity of the claimed motif by showing oligonucleotides having an unmethylated CpG dinucleotide are capable of inducing an immune response whereas oligonucleotides having the same sequence of nucleotides but a methylated C instead of an unmethylated C lose activity.

Applicants have presented a significant amount of data in the specification and asserted on the record that such data correlates with the scope of the claimed invention. Applicants have included many examples in the specification including induction of cytokines such as IL-6, IL-12

and IFN-gamma. The data in the application, includes that represented in Tables 1-3, which establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The combination of these changes in immune parameters was adequate to demonstrate to one of skill in the art at the time of the filing of the priority patent application that CpG oligonucleotides would be useful in the treatment of cancer. Applicants assert that a correlation between CpG and their use in the treatment of cancer is disclosed and enabled.

MPEP section 2164.02 teaches that

> "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
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> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)"

Applicants have presented data and asserted that it correlates with the scope of the claimed invention. The Examiner has not presented any objective evidence to demonstrate why it does not correlate. The teachings of Agrawal et al are not sufficient evidence to establish that it is impossible to predict the claimed invention. The fact that Agrawal et al teach certain nucleotides flanking the CpG motif are preferred for the induction of certain cytokines does not provide evidence that as of the priority date one of ordinary skill in the art would not have believed that the class of CpG oligonucleotides would function in the treatment of cancer as asserted by Applicants. Agrawal et. al., does not teach that some combinations of nucleotides surrounding the CpG motif will not work. He is just describing preferred compounds for certain purposes.

Crooke

In response to Applicants arguments regarding Crooke, the Examiner has made two points. First the examiner has dismissed applicants statement that whether or not CpG ODNs cross the

blood brain barrier is not relevant because according to the Examiner "claim 45 is drawn to a method treating brain cancer." Respectfully it is believed that the Examiner may not understand the instant invention. CpG oligonucleotides do not have direct effects on brain cells or tumor cells. CpG oligonucleotides stimulate immune cells to become activated and release factors that promote an immune response to kill the tumor cells. Thus, administration of a CpG ODN to a subject through a subcutaneous route, for example, could induce a systemic anti-tumor immune response that would eradicate not only tumor outside the CNS, but the activated immune cells could then cross the BBB and enter the CNS, attacking and controlling tumors therein, even though the CpG ODN itself never crossed the BBB. Additionally, one well recognized mode of administering an anti-tumor agent is by direct injection into the tumor. If one of skill in the art desired to promote an immune response in the immediate vicinity of the brain tumor he would simply need to inject within the site of the tumor. Such methods are performed in the art.

Secondly, the Examiner has asserted that "further Crooke et al further show that the release of cytokines, activation of complement and interference with clotting clearly poses dose limits if they are encountered in the clinic." Respectfully these statements are not relevant to the current invention. Firstly, Crooke is describing antisense technology. Antisense oligonucleotides are generally administered at a different dose than CpG oligonucleotides in order to produce a clinical effect, and thus it might be reasonable to expect different types of side effects. Additionally although Crooke describes the release of cytokines as being an undesirable effect of antisense oligonucleotides, this is not true of CpG oligonucleotides. CpG oligonucleotides function through the activation of immune cells to release cytokines. This is desirable. Antisense and CpG oligonucleotides work through completely distinct mechanisms. Finally, Crooke's concern with side effects associated with the administration of antisense oligonucleotides has not appeared to present a problem for either antisense oligonucleotides or CpG oligonucleotides. The tolerability of CpG oligonucleotides in humans has generally been good, with the most common side effects being transient injection site reactions and flu-like symptoms, as expected for an immune activator. In fact Agrawal et al on page 116 column 2 2nd full paragraph teaches that "CpG-antisense DNA molecules have been administered to humans up to doses of more than 20 mg kg^{-1} by continuous intravenous infusion, using various dosing regimens and schedules, for more than a year without

significant toxicity-related concerns." Currently there are a number of clinical trials being conducted with CpG oligonucleotides or that have already been completed. Clearly the FDA and other national regulatory agencies are convinced enough of the safety of the drug to allow clinical trials in human beings to be conducted around the world. It is respectfully requested that the rejection in view of Crooke be withdrawn. There is no basis for maintaining the rejection.

2. New references cited in support of Enablement Rejection

The Examiner has presented several new statements and references on pages 7-12 of the Office Action. Applicants address each of these arguments in detail below.

The Examiner has concluded that the "specification is viewed merely as an invitation to one skilled in the art to develop the claimed invention" and cites the following teaching from *Genentech v Novo Nordisk* 42 USPQ2d 10001 (CAFC 1997) "Tossing out the mere germ of an idea does not constitute an enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." (Office Action page 7-8)

Applicants have not "tossed out a mere germ of an idea." Rather, Applicants have made an important discovery, based on significant amounts of data, regarding a class of molecules that have enormous therapeutic utility. The data is included in the patent application. The invention is described throughout the specification.

The Examiner further stated that "supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks."

It is unclear what supporting documentation that the Examiner is referring to. Applicants have not attempted to correct any deficiencies of the specification by using supporting documentation. If the Examiner is referring to the clinical data references identified by Applicants, such references were put forth to rebut the Examiner's rejection based on post-filing references. They were not presented for the purpose of supplying any missing information from the specification. Applicant asserts that human clinical trial data is not required for a complete specification.

The Examiner has also stated on page 7 that 'reasonable correlation must exist between the scope of the claims and the scope of enablement set forth." As discussed above, Applicants have described the data included in the specification and asserted that it correlates. The Examiner has not provided any credible reason for why one of skill in the art at the time the patent application was filed would doubt that correlation.

On page 8 of the Office Action the Examiner has stated "defining a substance by its principle biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property.

Applicants cannot ascertain any relevance of the quoted statement to the claimed invention. Applicants have described a class of compounds in the claims by structure, not biological activity. The class of compounds is oligonucleotides having at least one unmethylated CpG motif a phosphate backbone modification and a length of 8-100 nucleotides. The Examiner is requested to clarify the purpose of this rejection.

The Examiner has cited Peterson et al (Eur J Cancer 2004, 40, 837-844) for the teaching that numerous agents showing activity in pre-clinical models don't have clinical activity. The reference does not teach anything about CpG oligonucleotides. Schuh (Toxicologic Pathology 2004, 32, 53-66) has been cited for similar reasons. The Examiner has indicated that Schuh teaches that reliance on mouse models may not be predictive of clinical success. Likewise, Bibby (Eur. J. Cancer 2004 40, 852-857) is cited to demonstrate that mouse models may not be predictive of clinical success. Saijo (Cancer Sci 2004; 95: 772-776) has been cited for the teaching that preclinical data doesn't always predict success in Phase III clinical trials.

These references are cited to establish that pre-clinical work is not always predictive of clinical success. However, the law is well established that a clinical trial is not required for enablement. If the Examiner is requiring clinical data to support the enablement at the time the patent application was filed, the Examiner is clearly incorrect. It is not appropriate for the PTO to determine if a drug is clinically successful. However, as mentioned previously CpG has shown promise so far in the clinical studies that have been undertaken.

The Wang et al reference (Exp. Opin. Biol Ther 2001, 1:277-290) was cited for the teaching that sometimes T-cell responses to vaccines do not lead to clinical tumor regression. The Wang et

al references concludes with "Of note, however, the vast majority of clinical trials were performed under less than optimal circumstances and often in patients with significantly advanced cancer. Furthermore, randomized Phase III trials with suitable control arms are only in the early stages." (page 286, 1st column.) Wang describes a summary of T cell directed cancer vaccines in melanoma. Applicants call the Examiner's attention to two articles describing the effects of CpG oligonucleotides in a melanoma system. Speiser et al J Clin Invest. 2005 Mar;115(3):739-46 and Appay V, et al J Immunol. 2006 Aug 1;177(3):1670-8. Copies are attached hereto as exhibit 1 and with IDS.

Kelland Eur J Cancer 2004, 40: 827-836 is cited for the teaching that there are limitations of a xenograft model for target driven drug development. The relevance of this reference is unclear since Applicants have not used a xenograft model and are not making any assertions about the correlation between a xenograft model and clinical success.

Accordingly, withdrawal of the rejection of claims 42-53 and 56-78 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: November 20, 2006

Respectfully submitted,

By _____

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